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ABNORMAL LEFT VENTRICULAR BETA-ADRENOCEPTOR-COUPLED ADENYLATE CYCLASE FUNCTION IN RIGHT HEART FAILURE.

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We have shown that as plasma norepinephrine increases in RV failure (RHF) produced by tricuspid avulsion and pulmonary artery constriction, the unstressed LV develops subnormal beta-adrenergic responsiveness. To determine whether the beta-adrenergic subsensitivity in LV was caused by excessive sympathetic stimulation, we administered oral nadolol (NAD, 40 mg/day) to RHF and sham-operated dogs for 5 weeks. We measured LV myocardial beta-receptor density (Bmax, fmol/mg) and dissociation constant (Kd, nM) using ^{3}H-dihydroalprenolol, maximum isoproterenol-stimulated adenylate cyclase (AC) activity (Vmax, pmol/mg/min) and the dose of isoproterenol needed to produce 50% of Vmax (Kact, μM). Results (mean±SE) were:

Group (N)	Bmax	Kd	Vmax	Kact
Sham (10)	113±7	2.22±0.18	73±3	0.24±0.01
Sham+NAD (10)	119±6	2.06±0.16	82±6	0.27±0.02
RHF (14)	111±6	2.91±0.17*	38±3*	0.45±0.01*
RHF+NAD (10)	130±7	1.98±0.17†	75±4†	0.26±0.01†

*p<0.05 vs. Sham; †p<0.05 vs. RHF.

Thus, while LV Bmax was unaffected, Kd and Kact increased and Vmax decreased in RHF, indicating a defective coupling between myocardial beta-receptor and AC in LV. Furthermore, since these changes were prevented by NAD, this abnormality probably is mediated via excessive adrenergic stimulation.

AEROBIC CAPACITY IN CHRONIC HEART FAILURE: A RANDOMIZED LONG-TERM COMPARISON OF CAPTOPRIL AND ENOXIMONE.

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Functional capacity was assessed in 20 patients with advanced chronic heart failure (NYHA: II=11, III=9) maintained on digitalis and diuretics randomized to either Enoximone (E) 100mg t.i.d. or Captopril (C) 12,5 mg t.i.d. At baseline (T_0), 4 weeks (T_1) and 6 months (T_2) after drug treatment, echocardiographic determinations of left ventricular diameters (LVEDD) systolic time intervals (QS2), and cardiopulmonary exercise testing with measurement of maximal oxygen uptake (VO2max) anaerobic threshold (VO2-AT), workload at AT (W-AT) and exercise time (t) was performed. Baseline examinations did not show a significant difference between both treatment groups.

	T_0		T_1		T_2	
	E	C	E	C	E	C
LVEDD	67±11	68±7	64±11	69±6	66±9	66±21
QS2	435±60	403±84	362±59*	384±5	371±58	417±74
VO2max	14.1±4	15.0±4	14.4±5	16.2±4	12.9±4	14.1±3
VO2-AT	13.1±4	12.5±3	12.0±3	14.3±4	10.0±3*	14.0±1
W-AT	62±26	71±17	65±17	75±19	45±16*	77±13
t(s)	369±100	420±141	393±137	520±156*	414±178	447±153

* = p<0.05

Clinical improvement was reported at T_1 in 6/10 E and in 3/10 C pts, at T_2 in 1/10 E but in 4/10 C pts. Captopril did not change left ventricular dimensions, systolic time intervals or determinants of aerobic capacity but improved exercise time at T_1 by 19% (p<0.05). Enoximone decreased QS2 both at T_1 and T_2 (p<0.03), however VO2 and workload at AT decreased at T_2 by 24% and 27% respectively (p<0,01); exercise time was not changed. No side effects or an abnormal arrhythmia profile were observed. It is concluded that in advanced chronic heart failure long-term treatment with enoximone compared to captopril does not prevent the progressive reduction of exercise capacity.

INAPPROPRIATE RENAL HEMODYNAMIC RESPONSE TO HYPERTONIC SALINE IN DOGS WITH EXPERIMENTAL ACUTE CONGESTIVE HEART FAILURE

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Increases in sodium delivery to the distal nephron reduces glomerular filtration rate (GFR) via tubuloglomerular feedback. This intrarenal regulator of GFR contributes to the maintenance of sodium and volume homeostasis and is known to be attenuated in states of central volume expansion. To test the hypothesis that tubuloglomerular feedback control of GFR is appropriately attenuated in congestive heart failure (CHF), hypertonic saline (HS) was given intrarenally in 6 dogs with acute CHF induced by rapid ventricular pacing. This model is associated with increases in RA pressure from 0.6±0.6 to 2.8±0.9 mmHg (p<0.05) and LA pressure from 3.3±0.6 to 10.9±2.2 mmHg (p<0.05). Seven non-paced dogs served as controls, and maintained normal cardiac filling pressures throughout the experiment.

	GFR (ml/min)		
	Pre-HS	Post-HS	%change
CHF	30.1±3.4	12.6±2.7*	58%
Controls	26.2±4.3	10.5±2.2*	63%

(* = p<0.05 HS vs pre-HS)

These studies demonstrate a maintenance of GFR in acute CHF despite associated reductions in cardiac output, mean arterial pressure and renal blood flow. Moreover, despite acute central volume overload in the CHF group, the GFR response to HS was not attenuated. This intact response to HS in acute CHF is inappropriate for the degree of central volume expansion and suggests a disturbance of GFR regulation which may contribute to sodium retention characteristic of acute CHF.

HOW DO VASODILATORS IMPROVE CARDIAC PERFORMANCE IN CHRONIC HEART FAILURE? INSIGHTS GAINED FROM TWO-DIMENSIONAL COLOR FLOW DOPPLER ECHOCARDIOGRAPHY.

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Previous studies have suggested that vasodilators improve cardiac performance by exerting beneficial effects on systolic and diastolic function, but hemodynamic events during vasodilator therapy correlate poorly with changes in systolic ejection or diastolic filling. To investigate the potential contribution of other factors, we performed right heart catheterization and 2-D color flow Doppler echocardiography in 17 patients with chronic heart failure (due to ischemic heart disease or dilated cardiomyopathy) before and after 3 days of therapy with either captopril or flosequinan. Changes in LV end-diastolic volume (EDV, ml), LV ejection fraction (EF, %), LA area (cm^2) and mitral regurgitant area (MRA, cm^2) during therapy were assessed blindly and were correlated with changes in cardiac output (CO, l/min), pulmonary wedge pressure (PWP, mm Hg) and systemic vascular resistance (SVR, d-s-c), where * = p < 0.05 (before vs after vasodilators):

	CO	PWP	SVR	EDV	EF	LA	MRA
Before	3.4	27	1901	370	17	24	5.1
After	3.9*	14*	1422*	368	18	25	3.6*

The hemodynamic improvement produced by vasodilators (↑ in CO and ↓ in PWP and SVR) was not accompanied by any change in EDV, EF or LA. The only echocardiographic variable altered by vasodilator therapy was MRA. Changes in CO and SVR were closely correlated with changes in MRA (r=0.63 and r=0.66, respectively), but not to changes in EDV (r=0.16 and r=-0.08) or EF (r=0.10 and r=-0.14). The change in MRA was the only predictor of the change in CO by stepwise regression analysis. Of note, changes in PWP did not correlate with any echocardiographic parameter.

The findings of this echocardiographic-hemodynamic study suggest that vasodilators exert their benefits in heart failure primarily by reducing mitral regurgitant flow rather than enhancing systolic function.